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RESEARCH ARTICLE

EVALUATION OF BONE MINERAL DENSITY IN YOUNG ADULT ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) PATIENTS: A single center Egyptian experience

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Abstract

Acute lymphoblastic leukemia (ALL) is a clonal hematological disease characterized by inadequate normal hematopoiesis secondary to excessive proliferation of leukemic blasts and their impaired differentiation. Bone health and the loss of bone density are important clinical concerns for patients with cancer who may be at risk for primary osteoporosis because of aging and other risk factors reference. They may have the added risk for cancer treatment-induced bone loss (CTIBL), which also could be termed secondary osteoporosis related to therapy and cancer as in (ALL).

This study was conducted on 25 Adult patients aged 20-45 years, with newly diagnosed ALL, presenting to Ain Shams University hospitals were recruited to this cross-sectional prospective study if they were eligible for induction therapy.

Bone mineral density (BMD) was evaluated by using dual-energy X-ray absorptiometry (DXA) for all studied subjects at presentation and at D28 for evaluable patients.

Measurements were performed at the lumbar spine (L2 to L4) and the left femoral neck using a Lunar DPX-L scanner. Bone mineral density was expressed in grams per square centimeter (g/cm2). Lumbar spine and femoral neck BMD was evaluated in all patients at diagnosis and after receiving induction chemotherapy. T-score was used to describe BMD (normal, osteopenia or osteoporosis) according to WHO classification .

None of the patients had osteoporosis either in the pre or post treatment evaluation (T-score < -2.5). Seven patient (28%) fulfilled the WHO criteria for osteopenia in the lumbar spine at diagnosis (T- score -1 to -2.5). At post-treatment evaluation, ten patients (40%) were found to have osteopenia as assessed at the lumbar spine. Yet the difference in bone density at the lumbar spine did not reach statistical significance (p-value >0.05). There was statistically significant reduction in the BMD at the left femoral neck, in the post treatment as compared to the pre treatment evaluation, with p-value <0.001

conclusion :Our results raised the issue that Skeletal morbidity, characterized by bone pain, osteonecrosis, fractures, loss of mobility, bone

deformation, or osteopenia, is frequently encountered in ALL patients affected by their hematological malignancy. Clinically important sites for evaluation of osteopenia/ osteoporosis in adult are the lumbar spine (L2-L4), and femoral neck.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a clonal hematological disease characterized by inadequate normal hematopoiesis secondary to excessive proliferation of leukemic blasts and their impaired differentiation. As a result, patients usually manifested symptoms related to bone marrow failure. ***(4).***

ALL is the predominant leukemia of childhood that runs an aggressive course and causes death within a few months if untreated ***(13)***.

The incidence of ALL in adults is relatively low. The etiology of most leukemia is uncertain. Although they are thought to be caused by a combination of environmental and genetic factor ***(3).***

Bone health and the loss of bone density are important clinical concerns for patients with cancer who may be at risk for primary osteoporosis because of aging and other risk factors (reference). They may have the added risk for cancer treatment-induced bone loss (CTIBL), which also could be termed secondary osteoporosis related to therapy and cancer as in ALL. ***(16).***

BMD loss with aging occurs because of hypogonadism and may progress to primary osteoporosis, whereas secondary osteoporosis, including CTIBL, results from chronic diseases, nutritional deficiencies, drugs, and other factors that negatively alter bone remodeling. The results in either case are increased PTH levels, greater bone resorption than synthesis, impaired neuromuscular functioning, and increased risk for falls and fractures ***(17).***

Osteopathy is not an uncommon initial manifestation of ALL. In a pediatric population, radiological abnormalities in the musculoskeletal system were demonstrated in about 40% of ALL patients ***(19).***

In contrast, skeletal morbidity is relatively rare in adult ALL. Because of its low incidence, the reported clinical experience of adult ALL with skeletal morbidity is rather limited, and the outlook for adult patients is still not conclusive ***(8).***

Bone pain, resulting from either bone erosion, periosteal lesions, or massive proliferation of blasts in the medullary canal and under the periosteum, is one of the most common presenting symptoms of ALL. In patients with ALL, who presented with prominent skeletal symptoms, they tended to have no lymphadenopathy, organomegaly, or leukocytosis ***(4).***

Childhood acute lymphoblastic leukemia (ALL) is the most common childhood leukemia type, in which overall survival (OS) at 5 years is more than 80% ***(15).*** Contrary to childhood ALL, the incidence of ALL in adult is lower and the prognosis is worse. Over the past decades, some therapeutic progress in adult ALL has been achieved with an average OS of 35%, which mainly rely on tailored therapeutic strategies according to the advances of prognostic factors and risk stratification ***(5)***.

Skeletal morbidity itself is an independent poor prognostic factor for OS and EFS. Patients with skeletal morbidity may be an independent disease entity with further investigation. A better understanding of the pathophysiology of ALL patients with skeletal morbidity and more intensive therapeutic strategies are needed for these patients ***(8).***

Aim of The Study: To assess bone mineral density in young adult patients with acute lymphoblastic leukemia (ALL) at presentation and after induction therapy, to determine whether disease and/or chemotherapy can affect bone density.

Patients and Methods:

This study was conducted on twenty-five (25) newly diagnosed adult ALL patients attending the Hematology/ Oncology unit of Ain Shams University hospitals, during the period from September 2012 till December 2014. They have all signed an informed consent and the study was approved by the local ethical committee. They were recruited to this cross-sectional prospective study if they were eligible for induction therapy for ALL to study BMD .

Inclusion criteria of patients:

- Young Adult patients (age ≥ 16 years ≤ 40 years).
- Diagnosis of all patients as ALL was carried on the basis of CBC finding, differential blood film, bone marrow aspiration, flow cytometry and cytogenetic analysis.

Exclusion criteria of patients:

- Patients who are not candidate to receive conventional induction chemotherapy due to bad general condition or concomitant systemic disease were excluded from this study.

Most of patients received induction Hoeltzer protocol chemotherapy(88%) While, who were diagnosed as mature B ALL (12%) received induction chemotherapy with dose intensive regimen of hyper fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) alternated with high dose cytarabine and methotrexate for a total of 8 induction and consolidation cycles. It is the only modern adult ALL treatment program where l-asparaginase is excluded totally . All courses with GCSF support, repeated every 3 weeks .Complete remission was defined as the absence of evidence of leukemia, which includes the absence of CNS or testicular disease, and to have bone marrow examination showing normal cellularity with fewer than 5% lymphoblast ***(6).***

Patients were followed up till they finished the first induction chemotherapy and Bone mineral density (BMD) is reevaluated.

Methods:

Every study participant was subjected to the following:

1) **Detailed history taking including**.
2) **Thorough clinical examination**
3) **Imaging Studies;** Chest X ray, Pelvi-Abdominal US, CT scan (brain, chest and pelvi-abdominal) to assess tumor volume, Testicular US,ECG
4) **Laboratory investigations including;** Complete Blood Count ,renal and hepatic profile ,coagulation profile and viral serology.Cerebrospinal fluid (CSF) examination for blast cells.
5) **Bone marrow examination:**

Bone marrow aspiration and examination of Leishman -stained films laying stress on % of blast, BM cellularity and dysplastic changes was performed at diagnoses and after induction therapy.

Myeloperoxidase-stained peripheral blood (PB) and bone marrow (BM) smears.

6) **Immunophenotyping** of BM aspirate was performed on EPICS XL coulter flow cytometry.

The panel of monoclonal antibodies included: common progenitor markers (CD34, HLADR), myeloid markers (CD13, CD33, CD14, CD15, CD61, MPO), B cell lymphoid markers (CD10, CD19, CD20, CD79a and CD79b) and T cell lymphoid markers (CD2, CD3, CD5, CD7).

According to immunophenotyping ALL cases were classified into B and T lymphoblastic leukaemia. B lymphoblastic leukaemia is subdivided to pro-B ALL, pre-B ALL and mature B ALL.

7) **Conventional cytogenetic analysis using G banding was** performed at diagnosis on bone marrow aspirate "standard karyotyping".

8) **Fluorescence in situ hybridization (FISH)** to detect BCR ABL gene.

9) **Assessment of Bone mineral density (BMD)** using Bone densitometry (DEXA) scan at diagnosis and after induction of therapy.

Assessment of bone mineral density by DEXA:

Bone mineral density (BMD) was measured by dual-energy x-ray absorptiometry (DEXA) at the left femoral neck and anteroposterior lumbar spine; with the use of a Lunar DPX-L densitometer. This was performed at Osteoporosis Prevention and Treatment Unit – Ain Shams University Hospital.

Bone mineral density was expressed in grams per square centimeter at the femoral neck and lumbar spine levels (L2-L4).

World Health Organization *(WHO, 1994).* Criteria for diagnosis of osteoporosis were used, based on measurements by DEXA ***(7).***

Interpretation

Interpretation of DEXA involves two results: the 'T-score' and 'Z-score'. The T-score is the number of standard deviations a patient's BMD differs from that of a healthy young adult of the same gender and ethnicity. The Z-score is the number of standard deviations a patient's BMD differs from an average person of the same age, gender, and ethnicity. Lower scores indicate lower bone density.

It is summarized as follows:

- Normal: A value of BMD within 1 standard deviation of the young adult reference mean (T-score ≥-1).
- Low bone mass (osteopenia): A value of BMD more than 1 standard deviation below the young adult mean, but less than 2 standard deviations below this value (T-score < -1 and > -2.5).
- Osteoporosis (OP): A value of BMD 2.5 standard deviations or more below the young adult mean (T-score ≤ -2.5).

Established (severe) OP is defined as a T-score less than –2.5 in the presence of a minimal trauma fracture.

- The Z-score indicates whether additional reasons for bone loss (besides aging) are likely. If the Z-score is less than –2.0, laboratory examinations for secondary causes of OP are indicated. However, a Z-score more than –2.0 does not exclude secondary OP. Further assessment should be guided by the medical history and clinical examination**(20)**

(5) Data collection and statistical analysis.

Statistical analysis

- Statistical Analysis of the data was performed by using the 16th version of Statistical Package of Social Science (SPSS).
- Quantitative data were expressed as mean (M) and standard deviation (SD).

- Qualitative data were expressed as frequency and percentage.
- Comparison between quantitative variables was done using t-test to compare two groups and ANOVA to compare 3 groups.
- Comparison of qualitative variables was done using Chi square test.
- Correlation coefficient was also done to find linear relation between different variables using Spearman's or Pearson's correlation co-efficient as indicated.
- Stepwise Multiple Regression Analysis of different predictor variables on a dependable variable using Beta standardized regression coefficients.
- Significance level was determined according to P value (Probability):
  P> 0.05 insignificant, P < 0.05 significant and P<0.01 highly significant.

RESULTS:

The current study was conducted on 25 adult patients recruited from the Hematology/ Oncology unit of Ain Shams University hospitals, Eleven patients (11/25) (44%) were females, while fourteen (14/25) patients were males (56%). Mean age was 30.32 (20-45 years), male: female ratio was 3:2. Presenting features include anemia (80%), bleeding tendency (52%), fever (52%) and hyper leucocytosis (32%). Extra medullary infiltration was detected in 3 patients, testis (n=1) and Central nervous system (n= 2).Sixteen patients (64%) had Pre-B ALL, one patient (4%) had Pro-B ALL, two patients (8%) had mature B ALL and six patients (24%) had T ALL. Clonal chromosomal abnormalities was detected in 4 patients (complex chromosomal abnormalities in one patient and t (9; 22) in 3 patients). 21 were evaluable at day +28. Seventeen patients (68%) were in complete remission and four patients (16%) had refractory leukaemia.

On follow up after 28 days, bone marrow aspirate showed that, seventeen patients (17/25) (68%) got complete hematological remission "defined as BM blasts less than 5%", four patients (4/25) (16%) were resistant "blast cells ≥ 20%.Four patients (4/25) (16%) died before day 28.cause of death varied between mucositis, DIC and cerebral hemorrhage, DVT and pulmonary embolism, toxic myocarditis and cardiogenic shock, fulminant hepatitis and liver cell failure in patient had hepatitis c virus, sever bronchopneumonia and ARDS, septicemia and septic shock.

Bone mineral density: None of the patients had osteoporosis either in the pre or post treatment evaluation (T-score < -2.5). Seven patients (28%) fulfilled the WHO criteria for osteopenia in the lumbar spine at diagnosis (T- score -1 to -2.5). At post-treatment evaluation, ten patients (40%) were found to have osteopenia as assessed at the lumbar spine.

In our study, There was highly statistically significant difference between the left femoral neck before and after treatment as regards mean BMD,T score and Z score, with p-value <0.001 (High significant) **.**While in Lumbar spine Bone Density there was no statistically significant difference between before and after treatment , with p-value >0.05 (non-significant)

Also, we detected the presence of a statistically significant difference between Lumbar spine densitometry categories (the prevalence of osteoporosis or osteopenia) before and after treatment, with p-value <0.05 (significant)

While in Left Femoral Neck densitometry categories (the prevalence of osteoporosis or osteopenia) there was no statistically significant difference between before and after treatment , with p-value >0.05 (non-significant) **(Table 1)**

Table (1): Bone mineral density BMD pre- and post treatment values at the lumbar spine and left femur neck.

Left Femur Bone Density			Paired Differences		t-test	
	Mean	**±SD**	**Mean**	**±SD**	**t**	**p-value**
Lt.femoral BMD pre treatment	1.33	0.15	0.11	0.10	5.384	**<0.001**
Lt.femoral BMD - post treatment	1.22	0.14				
Lt.femoral T score pre treatment	2.25	0.96	0.81	0.68	5.441	**<0.001**
Lt.femoral T score post treatment	1.44	1.05				
Lt.femoral Z score pre treatment	2.02	0.99	0.77	0.69	5.107	**<0.001**
Lt.femoral Z score post treatment	1.25	1.10				
Lumbar spine BMD pre- treatment	1.14	0.10	0.057	0.231	1.134	0.270
Lumbar spine BMD post- treatment	1.08	0.26				
Lumbar spine T score pre- treatment	-0.50	0.77	0.205	0.765	1.227	0.234
Lumbar spine T score post- treatment	-0.70	1.18				
Lumbar spine Z score pre- treatment	-0.92	0.86	0.005	0.762	0.029	0.977
Lumbar spine Z score post- treatment	-0.92	1.18				

Correlation statistics with other Laboratory Parameters:

Table (2): Correlation between **Left Femur Bone Density BMD** (before and after treatment) and laboratory parameters.

	LNF - BMD (Before)		**LNF - BMD (After)**	
	r	**p-value**	**r**	**p-value**
TLC	-0.197	0.345	-0.273	0.231
Blast (%)	-0.204	0.327	-0.432	**0.049 (S)**
RBC	-0.064	0.759	-0.162	0.484
Hb	-0.189	0.367	-0.339	0.132
Platelets	0.160	0.445	0.041	0.860
LDH	-0.449	**0.024 (S)**	-0.275	0.228
Uric acid	-0.169	0.420	-0.138	0.552
Day 1 aspirate	0.286	0.165	-0.053	0.819
Ca	0.058	0.783	-0.043	0.853
Corrected CA	0.239	0.251	0.178	0.440
G GT	-0.116	0.579	-0.077	0.742
Absolute blast count	-0.287	0.164	-0.524	**0.015 (S)**

This table shows:

- There was significantly negative correlation between LDH and **Left Femur Bone Density** (BMD) before treatment
- There was significantly negative correlation between Blast (%) and **Left Femur Bone Density** (BMD) after treatment

- There was Statistically significant and negative correlation between Absolute blast count and **Left Femur Bone Density** (BMD) post treatment.

Table (3): Correlation between **Left Femur Bone Density T-score** (before and after treatment) and laboratory parameters.

	LNF - T before		**LNF – T after**	
	r	**p-value**	**r**	**p-value**
TLC	-0.426	**0.034 (S)**	-0.440	**0.046 (S)**
Blast (%)	-0.401	**0.047 (S)**	-0.559	**0.008 (S)**
RBC	-0.214	0.304	-0.280	0.219
Hb	-0.308	0.134	-0.430	0.052
Platelets	0.199	0.341	0.094	0.685
LDH	-0.265	0.201	-0.208	0.365
Uric acid	-0.234	0.261	-0.195	0.397
Day 1 aspirate	0.035	0.869	-0.207	0.368
Ca	0.166	0.427	0.050	0.829
Corrected CA	0.330	0.108	0.208	0.366
G GT	-0.033	0.876	0.039	0.865
Absolute blast count	-0.535	**0.006 (S)**	-0.704	**<0.001(HS)**

This table shows:

- There was significantly negative correlation between TLC and **Left Femur Bone Density** (T score) before and after treatment
- There was significantly negative correlation between Blast (%) and **Left Femur Bone Density** (T score) before and after treatment

- There was Statistically significant and negative correlation between Absolute blast count and **Left Femur Bone Density** (T score) pre treatment.

- There was highly Statistically significant and negative correlation between Absolute blast count and **Left Femur Bone Density** (T score) post treatment.

Table (4): Correlation between **Left Femur Bone Density Z-score** (before and after treatment) and laboratory parameters.

	LNF - Z before		**LNF - Z After**	
	r	**p-value**	**r**	**p-value**
TLC	-0.400	**0.048 (S)**	-0.385	0.085
Blast (%)	-0.397	**0.049 (S)**	-0.525	**0.015 (S)**
RBC	-0.168	0.423	-0.289	0.204
Hb	-0.281	0.173	-0.438	**0.047 (S)**
Platelets	0.245	0.238	0.077	0.741
LDH	-0.266	0.200	-0.243	0.287
Uric acid	-0.199	0.340	-0.120	0.603
Day 1 aspirate	0.025	0.905	-0.199	0.388
Ca	0.147	0.484	0.009	0.968
Corrected CA	0.258	0.213	0.178	0.440
G GT	-0.105	0.619	-0.058	0.802
Absolute blast count	-0.537	0.006**(S)**	-0.626	0.002**(S)**

This table shows:

- There was significantly negative correlation between TLC and **Left Femur Bone Density** (Z score) before treatment.
- There was significantly negative correlation between Blast (%) and **Left Femur Bone Density** (Z score) before and after treatment.
- There was significantly negative correlation between Hb and **Left Femur Bone Density** (Z score) after treatment.
- There was Statistically significant and negative correlation between Absolute blast count and **Left Femur Bone Density** (Z score) pre treatment.

- There was Statistically significant and negative correlation between Absolute blast count and **Left Femur Bone Density** (Z score) post treatment

Table (5): Correlation between **Lumbar spine Bone Density BMD** (before and after treatment) and laboratory parameters .

	LS - BMD (Before)		**LS - BMD (After)**	
	r	**p-value**	**r**	**p-value**
TLC	0.006	0.978	-0.218	0.343
Blast (%)	0.085	0.685	-0.104	0.652
RBC	0.086	0.684	-0.092	0.693
Hb	0.077	0.716	-0.104	0.652
Platelets	-0.249	0.230	-0.805	**<0.001 (HS)**
LDH	-0.016	0.940	0.033	0.887
Uric acid	0.047	0.825	0.132	0.568
Day 1 aspirate	-0.081	0.699	0.201	0.383
Ca	0.172	0.411	0.347	0.124
Corrected CA	0.141	0.501	0.455	**0.038 (S)**
G GT	0.241	0.247	0.207	0.368
Absolute blast count	0.162	0.439	0.039	0.868

This table shows:
There was Statistically highly significant and negative correlation between platelet and **Lumbar spine Bone Density (BMD)** after treatment.
There was Statistically significant and positive correlation between corrected Ca and **Lumbar spine Bone Density (BMD)** after treatment.

Table (6): Correlation between **Lumbar spine Bone Density T-score** (before and after treatment) and laboratory parameters.

	LS - T before		**LS - T after**	
	r	**p-value**	**r**	**p-value**
TLC	0.070	0.740	-0.060	0.796
Blast (%)	0.140	0.505	0.105	0.651
RBC	0.155	0.460	0.131	0.572
Hb	0.126	0.549	0.207	0.367
Platelets	-0.302	0.142	-0.142	0.539
LDH	0.127	0.544	-0.171	0.459
Uric acid	0.175	0.402	0.171	0.458
Day 1 aspirate	0.054	0.796	-0.231	0.314
Ca	-0.023	0.912	0.005	0.981
Corrected CA	0.028	0.896	0.026	0.910
G GT	0.052	0.805	0.330	0.144
Absolute blast count	0.030	0.888	0.091	0.695

No significant correlation could be detected between **Lumbar spine Bone Density (T score)** at diagnosis and at follow up and any of the studied parameter.

Table (7): Correlation between **Lumbar spine Bone Density Z-score** (before and after treatment) and laboratory parameters.

	LS - Z before		LS - Z After	
	r	**p-value**	**r**	**p-value**
TLC	-0.112	0.594	-0.022	0.924
Blast (%)	0.019	0.926	0.110	0.634
RBC	0.198	0.343	0.166	0.473
Hb	0.170	0.417	0.214	0.352
Platelets	-0.228	0.273	-0.126	0.585
LDH	0.056	0.790	-0.171	0.459
Uric acid	0.111	0.596	0.208	0.366
Day 1 aspirate	-0.111	0.599	-0.201	0.381
Ca	0.152	0.467	0.052	0.823
Corrected CA	0.063	0.766	0.078	0.735
G GT	0.172	0.410	0.147	0.526
Absolute blast count	-0.100	0.635	0.125	0.589

No significant correlation could be detected between **Lumbar spine Bone Density (z score)** at diagnosis and at follow up and any of the studied parameter.

We tried to correlate the bone density (BMD,T score, Z score) in femoral neck and Lumbar spine Bone Density to several clinical variables in a multivariate analysis (age, sex, extra medullary disease, CT scan LN/HSM, CSF infiltration and Ph chromosome). However, we did not find any statistically significant correlation with any of the previous factors.

Discussion:

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease characterized by the accumulation and proliferation of clonal lymphoid progenitor cells in the bone marrow , periphery and / or extra medullary sites . As a consequence there is accumulation of an immature B- or T- cell clone in the bone marrow resulting in the suppression of normal hematopoiesis and in various extra medullary sites . **(13**).

Osteopathy is not an uncommon initial manifestation of ALL specially in pediatric population. (***19).***In contrast, the reported skeletal morbidity is less frequently reported in adult ALL. ***(8).*** In leukemia, the disruption of the bone marrow microenvironment and leukemic cell infiltrations results in osteopenia mediated by an expansion of osteoclasts causing increased bone reabsorption and a concomitant reduction of osteoblastic activity (***11).***

In our study, Bone Mineral Density was evaluated by **using dual-energy X-ray absorptiometry (DXA) in young** adult ALL patients to determine whether this disease and its therapy may have an effect on bone density.

Twenty-five (25) adult patients with newly diagnosed acute lymphoblastic leukaemia enrolled in our study, Eleven patients (44%) were females, while fourteen patients (56%) were males. They were diagnosed according to immuno-phenotypic criteria into sixteen patients (64%) with Pre-B ALL, one patient (4%) with Pro-B ALL, two patients (8%) with mature B ALL and six patients (24%) with T ALL. None of the patients had osteoporosis either in the pre or post treatment evaluation (T-score < -2.5). Seven patient (28%) fulfilled the WHO criteria for osteopenia in the lumbar spine at diagnosis (T- score -1 to -2.5). At post-treatment evaluation, ten patients (40%) were found to have osteopenia as assessed at the lumbar spine. Yet the

difference in bone density at the lumbar spine did not reach statistical significance (p-value >0.05). There was statistically significant reduction in the BMD at the left femoral neck, in the post treatment evaluation as compared to the pre- treatment evaluation, with p-value <0.001.

The treatment of ALL with steroid based intensive chemotherapy is associated with many deleterious side effects of therapy on bones including vertebral compression fractures, metabolic bone mineralization defects, osteopenia, and osteoporosis.

The current study confirms previously published reports that ALL patients are prone for osteopathic changes, with significant numbers having low bone mass density leading to increased risk of osteoporosis and fractures ***(10)(12).***

There are some explanations for the decrease in bone mineral density (BMD) in ALL patients. In normal hematopoiesis, hematopoietic stem cells (HSCs) are in balance with components of the hematopoietic microenvironment including osteoblastic cells, osteoclasts, mesenchymal cells, and vascular structures. In leukemia, invasion of leukemia cells results in osteopenia mediated by an expansion of osteoclasts causing increased bone reabsorption and a concomitant reduction of osteoblastic activity ***(18).***

When steroid based chemotherapy is started, changes in the electrolytes level, hormonal changes, cytokines and growth factors can suppress osteoblast activity leading to a limitation in bone mineralization throughout the treatment period.

This suggests that ALL patients might have abnormalities of bone metabolism before treatment, implying that the leukemic process itself is implicated as a mechanism for defective mineralization which is then aggravated by toxicity of steroid based therapy leading to decreased bone mass in long-term survivors.

We observed in our study that, there was no patient could be defined as having osteoporosis. There were **seven** (28%) patient who fulfilled the WHO criteria for osteopenia in the lumbar spine at diagnosis, but after treatment the number of osteopenia patients increase to ten (40%) patients as regard lumber spine. While, the Left Femoral Neck in the study groups as regards mean BMD,T score and Z score, was normal before and after treatment **.**

Measurement of bone mineralization by DXA scanning had been used long time ago for assessment of bone density. The radiation dose has been reported to be small and safe.(9)

Identification of other individual factors used in the treatment of ALL, which may account for the reductions in bone mass density, is difficult because of interactions between these variables and the fact that most therapy is rarely administered in isolation. For this reason, multiple regression analysis was used to explore possible interactions between variables in an attempt to find individual factors that may have an influence on bone mass density. We could not find any statistically significant correlation with any of the studied factors (age, sex, extra medullary disease, CT scan LN/HSM, CSF infiltration or cytogenetic anomalies). But There was Statistically significant and negative correlation between Absolute blast count, Blast (%) and Left Femur Bone Density (BMD) pre and post treatment.

Yet, There is no general agreement about a definite role of any of the risk factors for loss of BMD in the published literatures. ***(2)***, (***12) ,(1)***

Our results showed that BMD was initially low in considerable number of patients. Our results are consistent with the published international data that found that leukemic patients might have low BMD at diagnosis and additional loss may occur during therapy. ***(10)***

The different patterns of loss of BMD in the lumber spine and femur neck observed in our study were in agreement also with ***Marion et al. (2011).*** Although there is no clear explanation for this phenomenon, yet it might result from a particularly high sensibility of trabecular bone to changes in metabolic factors (calcium and vitamin D deficiency) or from a direct effect of the disease itself.

Few studies were trying to use serum parathyroid hormone-related protein (PTHrP) as a marker of hypercalcemia in adult leukemic patients for assessing disease status . ***In 1998, Naohisa et al,*** examined the relationship between serum PTHrP, LDH and calcium levels in three leukemic patients without renal failure, and found that normalization of serum PTHrP concentration preceded that of serum LDH levels after chemotherapy . They also found that elevation of the serum PTHrP level preceded elevation of the serum LDH level with leukemic cell proliferation. Serum LDH activity is commonly used as an indicator of tumor burden in Leukemic patients. These findings suggest that serum PTHrP levels may be more useful than serum LDH levels for confirming remission or for predicting relapse in leukemic patients with hypercalcemia

Conclusion:

Skeletal morbidity, characterized by bone pain, osteonecrosis, fractures, loss of mobility, bone deformation, or osteopenia, is frequently encountered in patients affected by ALL. Clinically important sites for evaluation of osteopenia/ osteoporosis in adult are the lumbar spine (L2-L4), and femoral neck.

Still , we are in need for further studies to assess Utility of measuring serum parathyroid hormone-related protein concentration in leukemic patients with hypercalcemia for assessing disease status, to draw more firm conclusions and to design screening and prophylactic programs.

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